Environmental Health Perspectives
Vol. 49, pp. 43-50, 1983

Acetylation, Deacetylation and Acyltransfer

by Charles M. King* and Irene B. Glowinski†

N-Substituted aromatic compounds can be metabolized in most species to *N*-acetylated derivatives that are themselves subject to further enzymatic transformations, including hydrolysis and *N,O*-acyltransfer. These proceses can either potentiate or ameliorate the biological responses to these *N*-substituted derivatives. Decreasing the levels of metabolites, such as arylhydroxylamines may, in some systems, reduce the probability of eliciting adverse biological effects. In others, arylhydroxamic acids produced by the acetylation of arylhydroxylamines may increase their potential for metabolic activation by *N,O*-acyltransfer. In the rabbit, rat and perhaps other species, the acetyl CoA-dependent *N*-acetyltransferase is also capable of activating arylhydroxamic acids by *N-O*-acyltransfer. These cytosolic organotriphosphate ester-resistant enzymes can utilize arylhydroxamic acid as a donor of the acetyl moiety in the acetyl transferase reaction and apparently are capable of activating arylhydroxamic acids because of their ability to *O*-acetylate the arylhydroxlamine. In mice, *N*-acetyltransferase and *N,O*-acetyltransferase seem not to exhibit this relationship. Enzymes from the microsomes of a number of species are also capable of activating arylhydroxamic acids. The particulate-bound enzymes are organotriphosphate ester-sensitive deacylases that are unable to form nucleic acid adducts on incubation with *N*-methoxy-*N*-acetylaminoarenes, substrates that are not capable of activation by *N,O*-acyltransfer. Thus, depending on the specificity of the enzymes involved, *N*-substituted aromatic compounds may be activated by *N,O*-acyltransfer during both the acetylation and deacylation process. The influence of this activation in the carcinogenic process is the object of continuing investigation.

Introduction

N-Substituted aromatic compounds are subject to enzymatic *N*-acetylation and further metabolism of the *N*-acetylated derivatives. Interest in the formation and disposition of these compounds comes from recognition that metabolism may modify the biological response to these agents by serving to reduce the levels of metabolites with undesirable properties (e.g., arylhydroxylamines) or to provide substrates (e.g., arylhydroxamic acids) for metabolic pathways which generate products that can adversely affect biological systems. Although metabolic oxidation of the methyl group of the *N*-acetyl moiety does occur, this pathway will not be addressed here, since the glycolamide does not appear to be involved in the tumorigenicity of arylamines (*1*). The purpose of this communication is to relate recent progress in our understanding of the interrelationships between *N*-acetylation, arylhydroxamic acid *N,O*-acyltransfer and deacetylation of *N*-substituted compounds, as these three reactions are capable of producing carcinogenic and mutagenic aromatic amine derivatives.

*Department of Chemical Carcinogenesis, Michigan Cancer Foundation, Detroit, MI 48201.
†Laboratory of Chemical Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, MD 20205.

N-Acetylation

Mechanism of Action and Distribution

N-Acetylation of aromatic amine carcinogens was first observed in rat liver slices using aminofluorene as substrate (*2*) (Fig. 1). Subsequent studies showed that other species were also capable of *N*-acetylating 2-aminofluorene (AF) as well as 4-aminobiphenyl and 2-naphthylamine (*3, 4*). The enzyme responsible for this metabolic step, acetyl CoA-dependent *N*-acetyltransferase (NAT), is the same enzyme as that responsible for the *N*-acetylation of aromatic amine drugs such as isoniazid and sulfamethazine (*5*). This is important in that Poirier et al. (*6*) postulated that *N*-arylhydroxylamines were involved in bladder cancer induction, whereas the acetylated derivatives were required for carcinogenesis in liver. The dog, unable to acetylate aromatic amines

Table 4. Relative cytosolic AHAT activities.[a]

	AF ($\times 10^{-11}$ mole) bound to tRNA on incubation with cytosol from various species									
Tissue	Rat	Hamster	Rabbit	Guinea pig	Monkey	Baboon	Pig	Human	Mouse	Dog and goat
Liver	111[b]	278[b]	371	9	56	58	32	12	5[b]	<2[b]
Kidney	29	11	4	12					<2	<2
Small intestine	36[b]	118[b]	43	12[b]	20			17	<2	<2
Colon	38	31	6	10	<2			5	<2	<2
Stomach	24[b]	36[b]	2	14	<2				<2	<2
Lung	13	18	3	3	<2			2	<2	
Mammary gland	10[b]									
Zymbal's gland	10[b]									
Spleen	7	4	2	3	<2				<2	<2
Brain	3	6	2	4						
Uterus			10[b]							
Bladder			20[b]							

[a]These data were obtained by use of standardized assay conditions (*23, 25, 39, 40-42*). The assay involved incubation of *N*-hydroxy-AAF (0.042 μmole) and tRNA (15 A_{260} units) with cytosol equivalent to 20 mg of tissue in pyrophosphate buffer (0.05*M*, pH 7.0) at 37°C for 20 min. (*43*).

[b]Tissue in which AF derivatives most commonly induce tumors.

cleic acid adduct formation on incubation of substrates with tissue cytosols (Table 4). Although activity is usually greatest in liver, a wide variety of other organs have demonstrable levels of AHAT. Importantly, dog tissues have neither AHAT nor NAT. Cytosolic AHATs with molecular weights of approximately 28,000 to 33,000 daltons are inhibited by reagents that react with sulfhydryl groups. Both *N*-acetylated and *N*-propionylated arylhydroxylamines can serve as substrates for the cytosolic AHAT and these reactions are not affected by organophosphate esterase inhibitors; *N*-formylated derivatives are poor substrates at best (*1, 18, 26, 27*). Mono-, di- and tricyclic arylhydroxamic acids, including derivatives of phenacetin, naphthalene, biphenyl, stilbene, fluorene and phenanthrene, can also serve as substrates such as phenacetin, the rats of adduct formation are considerably less than those for *N*-acetyltransfer as measured by the Booth assay (*29*).

Although cytosolic AHAT can transform its substrate to products that are mutagenic for Salmonella (*28-30*), it has been shown that the reactive product of the AHAT reaction is not responsible for this activity (*26, 30*). The mutagenicity may result from small quantities of hydroxylamines produced as a consequence of hydrolytic uncoupling of the acyltransfer process.

Studies of the structure-activity relationships have provided evidence that the organophosphate-insensitive AHAT of mammary gland of Sprague-Dawley derived female rats is involved in arylamine-induced tumors in this organ. Giganti and her colleagues have shown that direct treatment of the mammary gland with the hydroxamic acid *N*-hydroxy-*N*-acetyl-2-aminofluorene (*N*-hydroxy-AAF) is more effective in producing tumors than is the administration of the hydroxylamine, nitroso or amide derivatives (*31*). Subsequent experiments have employed arylhydroxamic acids that differ in their *N*-acyl moieties and, consequently, differ in their potential for activation by AHAT. The results suggest that rat mammary gland tumor susceptibility is related to the ability of arylhydroxamic acids to serve as substrates for AHAT, i.e., acetylated compounds are more active than formylated compounds (*1, 27, 32*). While the evidence of a causal role for AHAT in other tissues is less convincing, the major DNA adducts formed in all target tissues studied thus far are compatible with their formation via an acyltransfer mechanism.

Microsomal AHAT

Recent observations have disclosed that liver microsomes from a number of species have the ability to generate nucleic acid adducts on incubation with arylhydroxamic acids (Table 5) (*1, 18*). This activity yields arylamine-substituted guanine derivatives at carbon-8 without retention of the acyl group to give the same product as that produced by the cytosolic acyltransferases. However, unlike the case for the cytosolic enzymes, diethyl-*p*-nitrophenylphosphate (Paraoxon) is a potent inhibitor of the microsome-catalyzed activation. Resolution of solubilized guinea pig liver microsome preparations disclosed that two proteins are responsible for adduct formation (Table 6). These enzymes are readily distinguishable by differences in size and by their relative abilities to hydrolyze arylhydroxamic acids and amides. Substitution of the acidic hydrogen of the hydroxamic acid with a methyl group leads to reduction in adduct formation and provides evidence for activation by an acyltransfer mechanism (*18*).

Table 5. Species variation in the deacylation and AHAT activities of liver microsomes.

Species/strain	Deacylase, nmole/min/mg protein[a]		AHAT, nmole/min/mg protein[a]	
	With *N*-Hydroxy-AAF	With *N*-Hydroxy-FAF	With *N*-Hydroxy-AAF	With *N*-Hydroxy-FAF
Guinea pig (11)[b]	59	31	0.01	0.32
Hamster (2)	14.3	4.8	0.45	0.26
Rabbit[c]				
RR (1)	1.5	2.7	0.08	0.17
Rr (1)	3.9	5.0	0.09	0.18
rr (1)	7.5	11.6	0.14	0.64
Mouse				
A/J (2)	3.4	3.7	0.02	0.09
C57BL/6J (2)	4.0	3.2	0.03	0.21
Dog (3)	2.3	1.5	0.003	0.05
Rat (3)	1.9	1.3	0.02	0.18

[a]Means of the initial rates (*18*).

[b]The number of animals employed are given in parentheses.

[c]Rabbits were classified according to their arylamine acetylator phenotype (*16*): RR = homozygous rapid acetylator; Rr = heterozygous rapid acetylator; rr = slow acetylator.

Table 6. Relationship of AHAT from cytosols and microsomes.

Enzyme source	Type of AHAT[a]		
Rat			
Liver cytosol		II^{F}	III^{Ac}
Liver microsomes		$II^{F\ \&\ Ac}$	
Mammary gland cytosol		II^{F}	III^{Ac}
Guinea pig			
Liver cytosol	$I^{F\ \&\ Ac}$	II^{F}	III^{Ac}
Liver microsomes	$I^{F\ \&\ Ac}$	$II^{F\ \&\ Ac}$	

[a]The AHATs are classified according to the resolution of cytosols and solubilized microsomal preparations by gel filtration on Sephacryl S-200. The relative elution volumes of types I, II and III are 1.3 to 1.4, 1.55 to 1.65, and 1.8 to 1.9, respectively. These values, which are inversely related to molecular weight, are defined as the ratio of the volume required for elution of the peak enzyme activity to the volume at which excluded macromolecules first emerge from the column. Rat liver AHAT migrates with an apparent molecular weight of 28,000 on Sephadex G-100 (*23*). The AHAT activities were detected by assay of nucleic acid adduct formation on incubation with either the *N*-forymylated (F) or *N*-acetylated (Ac) *N*-2-fluorenylhydroxylamine. Type I and II AHAT are inhibited by diethyl-*p*-nitrophenylphosphate; Type III is resistant to this organophosphate (*1*, *18*).

Deacylation

Hydroxamic Acids

Both *N*-hydroxy-AAF (*33*, *34*) and *N*-hydroxy-*N*-formyl-2-aminofluorene (*N*-hydroxy-FAF) can be deacylated by enzymes present in the liver microsomal fractions of guinea pig, hamster, rabbit, mouse, dog and rat (Table 5) to produce the hydroxylamine, *N*-hydroxy-AF. As previously shown for *N*-hydroxy-AAF (*33*), guinea pig possesses the highest microsomal deacylase activity. All species tested, except guinea pig, have very low or nondetectable cytosolic deacylase activity for *N*-hydroxy-AAF. In contrast, *N*-hydroxy-FAF can be deacylated by cytosols of all species except hamster.

Guinea pig liver microsomes contain two enzymes capable of these reactions that differ in molecular weight as demonstrated by gel filtration (*18*, *35*). A wide range of acylated compounds are substrates for both enzymes (*35*). With respect to aromatic amines, the larger enzyme hydrolyzes *N*-hydroxy-AAF approximately 200 times faster than *N*-acetyl-2-aminofluorene (AAF), whereas the activities for hydrolysis of both compounds are about the same with the smaller enzyme (*18*, *35*). Recent work has shown that these purified microsomal deacylases are also capable of transforming *N*-hydroxy-AAF and *N*-hydroxy-FAF to derivatives that are capable of reacting with nucleic acid (see above). Both enzymes are inhibited by paraoxon. Guinea pig liver microsomes are also capable of deacetylating the *O*-glucuronide of *N*-hydroxy-AAF to yield metabolites that react with nucleic acids (*36*).

Jarvinen et al. (*35*) showed that in addition to microsomes from guinea pig liver, other tissues such as kidney and brain contain *N*-hydroxy-AAF deacylase activity. In an extensive survey of rat tissues, Irving (*37*) demonstrated that by far the highest *N*-hydroxy-AAF deacylation in this species occurs in the Zymbal's gland, an organ that is highly susceptible to carcinogenesis by AAF, *N*-hydroxy-AAF and other aromatic amines and amides. In contrast, the mammary gland, another rat tissue highly susceptible to carcinogenesis from these compounds, has very low deacylase activity.

Amides

Liver microsomes of many species also possess the ability to deacylate carcinogenic arylacetamides. Lower (*34*) showed that this is both substrate- and species-specific. Hamster and dog have relatively good activity for the deacylation of acetylaminobi-

phenyl and acetylaminofluorene; mouse has very high activity for acetylaminobiphenyl deacylation; and rat and guinea pig have very low activities for both. We have recently shown that guinea pig liver microsomes are also capable of deacylating *N*-formyl-2-aminofluorene as well as AAF (*18*). In addition to rat liver, rat intestine, a target organ for AAF-induced tumorigenesis, is capable of deacylating AAF as well as other acylaminofluorenes (*38*).

Relationship of *N*-Acetylation, *N,O*-Acyltransfer and Deacylation

As noted above, NAT and AHAT activities are identical in rabbit, but may not be related in mouse. While definitive experiments have not been carried out in rat, the association of cytosolic AHAT with the ability of arylhydroxamic acids to serve as acetyl donors in this species suggests that such a relationship does exist. It is probable that evolutionary changes have resulted in the development of a series of related NATs that differ both in their abilities to utilize hydroxamic acids as acetyl donors, and in their abilities to transfer the putative NAT-bound acyl group to the oxygen of the hydroxylamine, to produce a reactive *N*-acyloxyarylamine.

Recognition of the presence of other AHATs that are unrelated to the NAT enzymes came from experiments in which *N*-formylated hydroxamic acids were used to induce mammary gland tumors (*1, 27*). These studies identified a rat cytosolic enzyme that was capable of transforming *N*-formyl, but not *N*-acetyl or *N*-propionyl, derivatives to reactive products. The enzyme that activated the formyl compounds differed from the previously studied enzyme in that it was larger and was inhibited by diethyl-*p*-nitrophenylphosphate. Inhibition by an organophosphate prompted experiments to examine the possibility that this enzyme was a microsomal deacylaselike component that had been solubilized during the homogenization procedure (*18*). These efforts produced evidence (Table 6) that the organophosphate-sensitive enzyme had been released from microsomes with a concomitant loss of ability to activate *N*-acetylated derivatives. Similar experiments with guinea pig liver preparations demonstrated that the two microsomal AHATs of this organ also appear in cytosol. The sizes, sensitivities to inhibitors, and structure-activity relationships of these enzymes support the conclusion that microsomal deacylases can activate arylhydroxamic acids by *N,O*-acyltransfer. The great species variation in the structure-activity relationships of liver microsomal AHATs and deacylases suggests that evolution has resulted in families of enzymes that are analogous to those of NAT.

The presence of both deacylase and AHAT activities in the same enzyme preparation raises the question of the relative contributions of these two pathways to nucleic acid adduct formation. In rat microsomes, the rate of adduct formation after *N*-hydroxy-FAF metabolism is only 14% that of hydroxylamine formation (Table 5). However, in guinea pig liver microsomes, adduct formation after *N*-hydroxy-AAF metabolism is less than 0.02% that of the rate of hydrolysis, and most of the adduct formation potential is chromatographically separable from the deacylase activity. These data suggest that, while reaction of arylhydroxylamines with nucleic acid can occur at neutral pH, adduct formation in these enzyme-mediated systems occurs primarily as a consequence of the formation of products that are more reactive than the hydroxylamine. However, based on the results of studies with cytosolic AHAT, mutagenicity in Salmonella would be expected to be more influenced by hydroxylamine production than by the potential for adduct formation in cell-free systems. It is hoped that recognition of the relationship of these three metabolic pathways will be of aid in better defining their role in the induction of tumors by arylamines.

We thank Miss Debbie Scarborough for her assistance in the preparation of this manuscript.

This report was supported by grant CA 23386 from the National Cancer Institute.

REFERENCES

1. Shirai, T., Fysh, J. M., Lee, M. S., Vaught, J. B., and King, C. M. Relationship of metabolic activation of *N*-hydroxy-*N*-acylarylamines to biological response in the liver and mammary gland of the female CD rat. Cancer Res. 41: 4346-4353 (1981).
2. Peters, J. H., and Gutman, H. R. The acetylation of 2-aminofluorene and the deacetylation and concurrent reacetylation of 2-acetylaminofluorene by rat liver slices. J. Biol. Chem. 216: 713-726 (1955).
3. Lotlikar, P. D., and Luha, L. Enzymatic *N*-acetylation of *N*-hydroxy-2-aminofluorene by liver cytosol from various species. Biochem. J. 123: 287-289 (1971).
4. Lower, G. M., and Bryan, G. T. Enzymatic *N*-acetylation of carcinogenic aromatic amines by liver cytosol of species displaying different organ susceptibilities. Biochem. Pharmacol. 22: 1581-1588 (1973).
5. Glowinski, I. B., Radtke, H. E., and Weber, W. W. Genetic variation in *N*-acetylation of carcinogenic arylamines by human and rabbit liver. Mol. Pharmacol. 14: 940-949 (1978).
6. Poirier, L. A., Miller, J. A., and Miller, E. C. The *N*- and ring hydroxylation of 2-acetylaminofluorene and the failure to detect *N*-acetylation of 2-aminofluorene in the dog. Cancer Res. 23: 790-800 (1963).
7. Kadlubar, F. F., Miller, J. A., and Miller, E. C. Hepatic microsomal *N*-glucuronidation and nucleic acid binding of *N*-hydroxylamines in relation to urinary bladder carcinogenesis. Cancer Res. 37: 805-814 (1977).
8. Radomski, J. L., Hearn, W. L., Radomski, T., Moreno, H., and Scott, W. E. Isolation of the glucuronic acid conjugate

of *N*-hydroxy-4-aminobiphenyl from dog urine and its mutagenic activity. Cancer Res. 37: 1757-1762 (1977).
9. Hearse, D. J., and Weber, W. W. Multiple *N*-acetyltransferases and drug metabolism. Biochem. J. 132: 519-526 (1973).
10. Glowinski, I. B., and Weber, W. W. Genetic regulation of aromatic amine *N*-acetylation in inbred mice. J. Biol. Chem. 257: 1424-1430 (1982).
11. Glowinski, I. B., and Weber, W. W. Biochemical characterization of genetically variant aromatic amine *N*-acetyltransferases in A/J and C57BL/6J mice. J. Biol. Chem. 257: 1431-1437 (1982).
12. Drayer, D. E., and Reidenberg, M. M. Clinical consequences of polymorphic acetylation of basic drugs. Clin. Pharm. Ther. 22: 251-258 (1977).
13. Lunde, P. K. M., Frislid, K., and Hansteen, V. Disease and acetylation polymorphism. Clin. Pharmacokinet. 2: 182-197 (1977).
14. Lower, G. M. Metabolic factors involved in bladder carcinogenesis (abstract). National Bladder Cancer Project Investigators Workshop, Sarasota, FL, 1978, p. 14.
15. Lower, G. M., Nilsson, T., Nelson, C. E., Wolf, H., Gamsky, T. E., and Bryan, G. T. *N*-acetyltransferase phenotype and risk in urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. Environ. Health Perspect. 29: 71-79 (1979).
16. Glowinski, I. B., Weber, W. W., Fysh, J. M., Vaught, J. B., and King, C. M. Evidence that arylhydroxamic acid *N,O*-acyltransferase and the genetically polymorphic *N*-acetyltransferase are properties of the same enzyme in rabbit liver. J. Biol. Chem. 255: 7883-7890 (1980).
17. Brusick, D., Bakshi, M. K., and Jagannath, D. R. The application of *in vitro* mutagenesis techniques to investigations of comparative metabolism in mice. In: *In Vitro* Metabolic Activation in Mutagenesis Testing (F. deSerres, J. R. Fouts, J. R. Bend and R. M. Philpot, Eds.), Elsevier, North Holland, Amsterdam, 1976, pp. 125-141.
18. Glowinski, I. B., Savage, L., Lee, M. S., and King, C. M. Relationship between nucleic acid adduct formation and deacylation of arylhydroxamic acids. Carcinogenesis, in press.
19. King, C. M., and Phillips, B. Enzyme-catalyzed reactions of the carcinogen *N*-hydroxy-2-fluorenylacetamide with nucleic acid. Science 159: 1351-1353 (1968).
20. King, C. M., and Phillips, B. *N*-hydroxy-2-fluorenylacetamide: reaction of the carcinogen with guanosine, ribonucleic acid, deoxyribonucleic acid, and protein following enzymatic deacetylation or esterification. J. Biol. Chem. 224: 2609-2616 (1969).
21. DeBaun, J. E., Rowley, J. Y., Miller, E. C., and Miller, J. R. Sulfotransferase activation of *N*-hydroxy-2-acetylaminofluorene in rodent livers susceptible and resistant to this carcinogen. Proc. Soc. Exptl. Biol. Med. 129: 268-273 (1968).
22. Bartsch, H., Dworkin, M., Miller, J. A., and Miller, E. C. Electrophilic *N*-acetoxyaminoarenes derived from carcinogenic *N*-hydroxy-*N*-acetylaminoarenes by enzymatic deacetylation and transacetylation in liver. Biochim. Biophys. Acta 286: 262-298 (1972).
23. King, C. M. Mechanism of reaction, tissue distribution and inhibition of arylhydroxamic acid acyltransferase. Cancer Res. 34: 1503-1516 (1974).
24. Booth, J. Acetyltransfer in arylamine metabolism. Biochem. J. 100: 745-753 (1966).
25. King, C. M., and Olive, C. W. Comparative effects of strain, species and sex on the acyltransferase- and sulfotransferase-catalyzed activations of *N*-hydroxy-*N*-2-fluorenylacetamide. Cancer Res. 35: 906-912 (1975).
26. Weeks, C. E., Allaben, W. T., Tresp, N. M., Louie, S. C., Lazear, E. J., and King, C. M. Effects of structure of *N*-hydroxy-*N*-2-fluorenylacylamides on arylhydroxamic acid acyltransferase, sulfotransferase, and deacetylase activities, and on mutation in *Salmonella typhimurium* TA-1538. Cancer Res. 40: 1204-1211 (1980).
27. Allaben, W. T., Weeks, C. E., Tresp, N. C., Louie, S. C., Lazear, E. J., and King, C. M. Mammary tumor induction in the rat by *N*-acyl-*N*-2-fluorenyl-hydroxylamines: structure-activity relationship. Carcinogenesis 3: 233-240 (1982).
28. Morton, K. C., King, C. M., and Baetcke, K. P. Metabolism of benzidine to *N*-hydroxy-*N,N'*-diacetylbenzidine and subsequent nucleic acid binding and mutagenicity. Cancer Res. 39: 3107-3113 (1979).
29. Vaught, J. B., McGarvey, P. B., Lee, M. S., Wang, C. Y., Linsmaier-Bednar, E. M., and King, C. M. Activation of *N*-hydroxyphenacetin to mutagenic and nucleic acid-binding metabolites by acyltransfer, deacylation, and sulfate conjugation. Cancer Res. 41: 3424-3429 (1981).
30. Weeks, C. E., Allaben, W. T., Louie, S. C., Lazear, E. J., and King, C. M. Role of arylhydroxamic acid acyltransferase in the mutagenicity of *N*-hydroxy-*N*-fluorenylacetamide in *Salmonella typhimurium*. Cancer Res. 38: 613-618 (1978).
31. Malejka-Giganti, D., and Gutmann, H. R. *N*-hydroxy-2-fluorenylacetamide, an active intermediate of the mammary carcinogen *N*-hydroxy-2-fluorenylbenzenesulfonamide (38980). Proc. Soc. Exp. Biol. Med. 150: 92-97 (1975).
32. Allaben, W. T., Burger, G. T., Weis, C. T., and Gamper, J. T. *N*-Hydroxy-*N*-2-acylaminofluorene induced mesotheliomas, mammary adenocarcinomas, and Zymbal's gland carcinomas in Sprague-Dawley rats. Proc. Am. Assoc. Cancer Res. 22: 101 (1981).
33. Irving, C. C. Enzymatic deacetylation of *N*-hydroxy-2-acetylaminofluorene by liver microsomes. Cancer Res. 26: 1390-1396 (1966).
34. Lower, G. M., and Bryan, G. T. Enzymatic deacetylation of carcinogenic arylacetamides by tissue microsomes of the dog and other species. J. Toxicol. Environ. Health 1: 421-432 (1976).
35. Jarvinen, M., Santti, R. S. S., and Hopsu-Havu, V. K. Partial purification and characterization of two enzymes from guinea pig liver microsomes that hydrolyze carcinogenic amides, 2-acetylaminofluorene and *N*-hydroxy-2-acetylaminofluorene. Biochem. Pharmacol. 20: 2971-2982 (1971).
36. Cardona, R. A., and King, C. M. Activation of the *O*-glucuronide of the carcinogen *N*-hydroxy-*N*-2-fluorenylacetamide by enzymatic deacetylation *in vitro*: formation of fluorenylamine-tRNA adducts. Biochem. Pharmacol. 25: 1051-1056 (1976).
37. Irving, C. C. Species and tissue variations in the metabolic activation of aromatic amines. In: Carcinogenesis: Identification and Mechanisms of Action (A. C. Griffin and C. R. Shaw, Eds.), Raven Press, New York 1979, pp. 211-227.
38. Nagasawa, H. T. and Gutmann, H. R. A note on the deacylation of the carcinogen 2-acetamidofluorene and related compounds by rat liver and intestine. Biochim. Biophys. Acta 25: 186-189 (1957).
39. King, C. M., Traub, N. R., Lortz, Z. M., and Thissen, M. R. Metabolic activation of arylhydroxamic acid, *N,O*-acyltransferase by rat mammary gland. Cancer Res. 39: 3369-3372 (1979).
40. King, C. M., Olive, C. W., and Cardona, R. A. Activation of carcinogenic arylhydroxamic acids by acyltransferase of human tissues. J. Natl. Cancer Inst. 55: 285-287 (1975).
41. Beland, F. A., Allaben, W. T., and Evans, F. E.

Acyltransferase-mediated binding of *N*-hydroxyarylamides to nucleic acids. Cancer Res. 40: 834-840 (1980).
42. King, C. M., and Allaben, W. T. Arylhydroxamic acid acyltransferase. In: Enzymatic Basis of Detoxication, Vol. II (W. B. Jakoby, Ed.), Academic Press, New York, 1980, pp. 187-197.
43. Weber, W. W., and King, C. M. Rabbit liver *N*-acetyltransferase and arylhydroxamic acid acyltransferase. In: Methods in Enzymology, Vol. 77 (W. B. Jakoby, Ed.) Academic Press, New York, 1981, pp. 272-280.